Andrew Freistein 10/788,859

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NEWS	1		Web Page URLs for STN Seminar Schedule - N. America
NEWS	2		"Ask CAS" for self-help around the clock
NEWS	3	JUL 20	Powerful new interactive analysis and visualization software, STN AnaVist, now available
NEWS	4	AUG 11	STN AnaVist workshops to be held in North America
NEWS	5	AUG 30	CA/CAplus -Increased access to 19th century research documents
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NEWS	7	SEP 09	ACD predicted properties enhanced in REGISTRY/ZREGISTRY
NEWS	8	OCT 03	MATHDI removed from STN
NEWS	9	OCT 04	CA/CAplus-Canadian Intellectual Property Office (CIPO) added to core patent offices
NEWS	10	OCT 06	STN AnaVist workshops to be held in North America
NEWS	11	OCT 13	New CAS Information Use Policies Effective October 17, 2005
NEWS	12	OCT 17	STN(R) AnaVist(TM), Version 1.01, allows the export/download of CAplus documents for use in third-party analysis and visualization tools
NEWS	13	OCT 27	Free KWIC format extended in full-text databases
NEWS	14	OCT 27	DIOGENES content streamlined
NEWS	15	OCT 27	EPFULL enhanced with additional content

NEWS EXPRESS	JUNE 13 CURRENT WINDOWS VERSION IS V8.0, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 13 JUNE 2005
NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS INTER	General Internet Information
NEWS LOGIN	Welcome Banner and News Items
NEWS PHONE	Direct Dial and Telecommunication Network Access to STN
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FILE 'HOME' ENTERED AT 08:57:37 ON 14 NOV 2005

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=> file reg
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.21       0.21

FILE 'REGISTRY' ENTERED AT 08:57:46 ON 14 NOV 2005
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STRUCTURE FILE UPDATES:   13 NOV 2005  HIGHEST RN 867336-65-0
DICTIONARY FILE UPDATES:  13 NOV 2005  HIGHEST RN 867336-65-0

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TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

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**********************************************************************
*                                                                    *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,   *
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Structure search iteration limits have been increased.  See HELP SLIMITS
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REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

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Uploading C:\Program Files\Stnexp\Queries\10788859\FAOM\c.str
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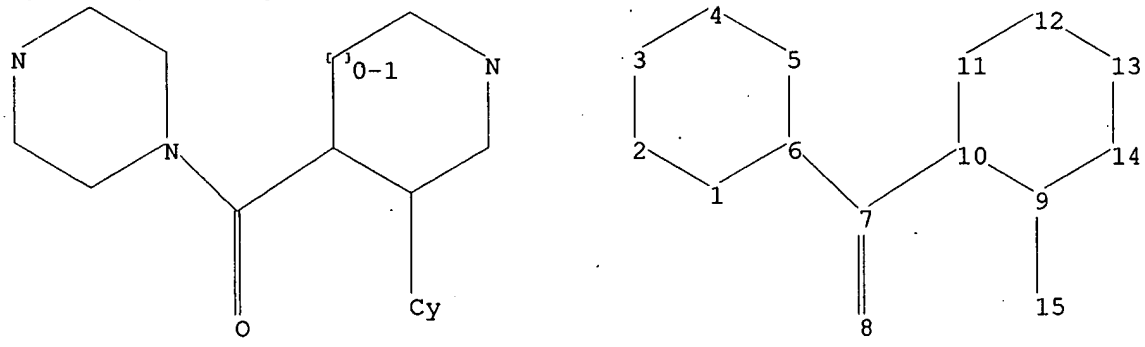
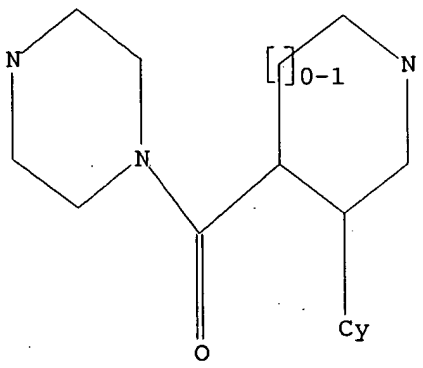


chain nodes :
7 8 15
ring nodes :
1 2 3 4 5 6 9 10 11 12 13 14
chain bonds :
6-7 7-8 7-10 9-15
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 9-10 9-14 10-11 11-12 12-13 13-14
exact/norm bonds :
1-2 1-6 2-3 3-4 4-5 5-6 6-7 7-8 9-10 9-14 9-15 10-11 11-12 12-13
13-14
exact bonds :
7-10

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:CLASS 8:CLASS 9:Atom 10:Atom
11:Atom 12:Atom 13:Atom 14:Atom 15:Atom

L1 STRUCTURE UPLOADED

=> d
L1 HAS NO ANSWERS
L1 STR



Structure attributes must be viewed using STN Express query preparation.

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SAMPLE SEARCH INITIATED 08:58:12 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 828 TO ITERATE

100.0% PROCESSED 828 ITERATIONS 19 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 14834 TO 18286
PROJECTED ANSWERS: 119 TO 641

L2 19 SEA SSS SAM L1

=> s l1 full
FULL SEARCH INITIATED 08:58:17 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 16232 TO ITERATE

100.0% PROCESSED 16232 ITERATIONS 534 ANSWERS
SEARCH TIME: 00.00.01

L3 534 SEA SSS FUL L1

=> file hcaplus
COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	161.33	161.54

FILE 'HCAPLUS' ENTERED AT 08:58:22 ON 14 NOV 2005
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FILE COVERS 1907 - 14 Nov 2005 VOL 143 ISS 21
FILE LAST UPDATED: 13 Nov 2005 (20051113/ED)

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This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l3
L4 15 L3

=> d ibib 1-5

L4 ANSWER 1 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:395265 HCAPLUS
DOCUMENT NUMBER: 142:463753
TITLE: Preparation of piperazinyl carboxamide and related cyclic homologs as ligands of melanocortin receptors and compositions and methods related thereto
INVENTOR(S): Chen, Chen; Tran, Joe Ahn; Tucci, Fabio C.; Chen, Wei-Chuan C.; Jiang, Wanlong; Marinkovic, Dragan; Arellano, Melissa; White, Nicole
PATENT ASSIGNEE(S): Neurocrine Biosciences, Inc., USA
SOURCE: PCT Int. Appl., 166 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005040109	A1	20050506	WO 2004-US35343	20041022
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2005192286	A1	20050901	US 2004-972064	20041022
PRIORITY APPLN. INFO.:			US 2003-513626P	P 20031022

OTHER SOURCE(S): MARPAT 142:463753
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:965987 HCAPLUS
DOCUMENT NUMBER: 141:411221
TITLE: Preparation of piperazine melanocortin receptor-specific compounds
INVENTOR(S): Sharma, Shubh D.; Shi, Yi-qun; Rajpurohit, Ramesh; Wu, Zhijun; Purna, Papireddy; Shadiack, Annette M.; Burris, Kevin D.
PATENT ASSIGNEE(S): Palatin Technologies, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 69 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 8
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004224957	A1	20041111	US 2004-837519	20040430
WO 2004098602	A1	20041118	WO 2004-US13803	20040503
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2005130988	A1	20050616	US 2005-36282	20050114
US 2005124636	A1	20050609	US 2005-40838	20050121
US 2005176728	A1	20050811	US 2005-99814	20050405
PRIORITY APPLN. INFO.:			US 2003-467442P	P 20030501
			US 2004-546393P	P 20040219
			US 2001-311404P	P 20010810
			WO 2002-US25574	A2 20020812
			US 2003-474497P	P 20030530
			US 2004-536606P	P 20040114
			US 2004-538100P	P 20040121
			US 2004-761889	A2 20040121
			US 2004-762079	A2 20040121
			US 2004-559741P	P 20040405
			US 2004-563739P	P 20040419
			US 2004-837519	A 20040430

OTHER SOURCE(S): MARPAT 141:411221

L4 ANSWER 3 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:756685 HCAPLUS
DOCUMENT NUMBER: 141:277640
TITLE: Preparation of acylated piperazine derivatives as melanocortin -4 receptor agonists for the treatment of obesity, diabetes mellitus and sexual dysfunction, and pharmaceutical compositions thereof
INVENTOR(S): Bakshi, Raman K.; Guo, Liangqin; Hong, Qingmei; Nargund, Ravi P.; Pollard, Patrick G.; Sebhat, Iyassu K.; Ujjainwalla, Feroze; Ye, Zhixiong
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 187 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004078717	A1	20040916	WO 2004-US7713	20040227
W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ, MZ, NA, NI				
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US 2004204398	A1	20041014	US 2004-788859	20040227
PRIORITY APPLN. INFO.:			US 2003-451502P	P 20030303
			US 2003-515943P	P 20031030

OTHER SOURCE(S): MARPAT 141:277640
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:756684 HCAPLUS
DOCUMENT NUMBER: 141:277639
TITLE: Preparation of acylated piperazine derivatives as melanocortin-4 receptor agonists for the treatment of obesity, diabetes mellitus and sexual dysfunction, and pharmaceutical compositions thereof
INVENTOR(S): Bakshi, Raman K.; Hong, Qingmei; Nargund, Ravi P.; Pollard, Patrick G.; Sebhat, Iyassu K.; Ujjainwalla, Feroze; Ye, Zhixiong
PATENT ASSIGNEE(S): Merck & Co. Inc., USA
SOURCE: PCT Int. Appl., 76 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004078716	A1	20040916	WO 2004-US5982	20040227
W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ, MZ, NA, NI				
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US 2004204398	A1	20041014	US 2004-788859	20040227
PRIORITY APPLN. INFO.:			US 2003-451502P	P 20030303
			US 2003-515943P	P 20031030

OTHER SOURCE(S): MARPAT 141:277639
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:652533 HCAPLUS
DOCUMENT NUMBER: 141:191073
TITLE: Preparation of piperazines as melanocortin-specific agonists, antagonists, or mixed agonists and antagonists.
INVENTOR(S): Sharma, Shubh D.; Shi, Yi-qun; Wu, Zhijun; Rajpurohit, Ramesh
PATENT ASSIGNEE(S): Palatin Technologies, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 70 pp., Cont.-in-part of Appl. No. PCT/US02/25574.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 8
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004157264	A1	20040812	US 2004-762079	20040121
WO 2003013571	A1	20030220	WO 2002-US25574	20020812
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WO 2005102340	A1	20051103	WO 2004-US1462	20040121
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US 2005130988	A1	20050616	US 2005-36282	20050114
US 2005124636	A1	20050609	US 2005-40838	20050121
US 2005176728	A1	20050811	US 2005-99814	20050405

PRIORITY APPLN. INFO.:

US 2001-311404P	P	20010810
WO 2002-US25574	A2	20020812
US 2003-474497P	P	20030530
US 2003-467442P	P	20030501
US 2004-536606P	P	20040114
US 2004-538100P	P	20040121
US 2004-761889	A2	20040121
US 2004-762079	A2	20040121
US 2004-546393P	P	20040219
US 2004-559741P	P	20040405
US 2004-563739P	P	20040419

L4 ANSWER 5 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

US 2004-837519 A2 20040430

OTHER SOURCE(S): MARPAT 141:191073

=> d ibib abs hitstr 1-2

L4 ANSWER 1 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:395265 HCAPLUS
DOCUMENT NUMBER: 142:463753
TITLE: Preparation of piperazinyl carboxamide and related cyclic homologs as ligands of melanocortin receptors and compositions and methods related thereto
INVENTOR(S): Chen, Chen; Tran, Joe Ahn; Tucci, Fabio C.; Chen, Wei-Chuan C.; Jiang, Wanlong; Marinkovic, Dragan; Arellano, Melissa; White, Nicole
PATENT ASSIGNEE(S): Neurocrine Biosciences, Inc., USA
SOURCE: PCT Int. Appl., 166 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005040109	A1	20050506	WO 2004-US35343	20041022
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
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US 2005192286	A1	20050901	US 2004-972064	20041022
PRIORITY APPLN. INFO.:			US 2003-513626P	P 20031022
OTHER SOURCE(S):	MARPAT 142:463753			

GI

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:965987 HCAPLUS
DOCUMENT NUMBER: 141:411221
TITLE: Preparation of piperazine melanocortin receptor-specific compounds
INVENTOR(S): Sharma, Shubh D.; Shi, Yi-qun; Rajpurohit, Ramesh; Wu, Zhijun; Purma, Papireddy; Shadiack, Annette M.; Burris, Kevin D.
PATENT ASSIGNEE(S): Palatin Technologies, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 69 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 8
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004224957	A1	20041111	US 2004-837519	20040430
WO 2004098602	A1	20041118	WO 2004-US13803	20040503
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
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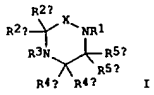
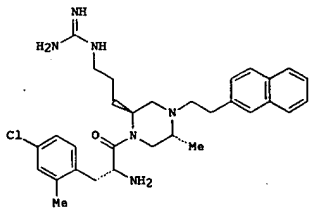
US 2005130988	A1	20050616	US 2005-36282	20050114
US 2005124636	A1	20050609	US 2005-40838	20050121
US 2005176728	A1	20050811	US 2005-99814	20050405
PRIORITY APPLN. INFO.:			US 2003-467442P	P 20030501
			US 2004-546393P	P 20040219
			US 2001-311404P	P 20010810
			WO 2002-US25574	A2 20020812
			US 2003-474497P	P 20030530
			US 2004-536606P	P 20040114
			US 2004-538100P	P 20040121
			US 2004-761889	A2 20040121
			US 2004-762079	A2 20040121
			US 2004-559741P	P 20040405
			US 2004-563739P	P 20040419
			US 2004-837519	A 20040430
OTHER SOURCE(S):	MARPAT 141:411221			

GI

L4 ANSWER 2 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



I



II

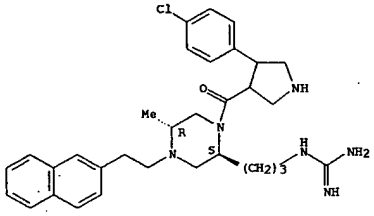
AB The invention relates to amino acid-derived piperazine compds. I [X is CH2, CO or CS; R1 is -L1-J; one of R2a and R2b is -L2-W and the other is H; R3 is -L3-Q; L1 is a bond or a linker unit comprising from one to eight backbone atoms selected from carbon, sulfur, oxygen or nitrogen; J is a ring structure, e.g., an (un)substituted aromatic or non-aromatic carbocyclic ring; L2 is a bond or (CH2)1-6; W is a heteroatom unit with at least one cationic center, hydrogen bond donor or acceptor (at least one heteroatom is nitrogen or oxygen); L3 is a bond or a linker unit comprising from one to nine backbone atoms selected from carbon, sulfur, oxygen or nitrogen; Q is (un)substituted Ph or naphthyl; one or two of R4a, R4b, R5a and R5b are independently -L2-W or an aliphatic chain and the others are H, provided that at least one of R4a and R4b and at least one of R5a and R5b is H], including enantiomers, stereoisomers, diastereoisomers or pharmaceutically-acceptable salts, which bind with high affinity to one or more melanocortin receptors (MCR) and may be employed for treatment of melanocortin receptor-associated conditions or disorders. Thus, piperazine derivative II was prepared via reactions of 2-naphthylacetic acid, (R)-(-)-2-amino-1-propanol, Fmoc-L-Arg(Boc)2-OH (Fmoc = fluorenylmethoxycarbonyl, Boc = tert-butoxycarbonyl), and Boc-D-4-chloro-2-methyl-L-phenylalanine. Compound II was shown to be a partial agonist as to MC4-R and in rats caused a decrease in food intake (administration 2 h prior to food presentation) and induced penile erection at 0.3-30 μg/Kg.

IT 791625-06-4P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of piperazine melanocortin receptor-specific compds.)

RN 791625-06-4 HCAPLUS
CN 2-Piperazinepropanamine, N-(aminoiminomethyl)-1-[[4-(4-chlorophenyl)-3-pyrrolidinyl]carbonyl]-5-methyl-4-[2-(2-naphthalenyl)ethyl]-, (2S,5R)-

L4 ANSWER 2 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
(9CI) (CA INDEX NAME)

Absolute stereochemistry.



=> d ibib abs hitstr 5-15

L4 ANSWER 5 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN

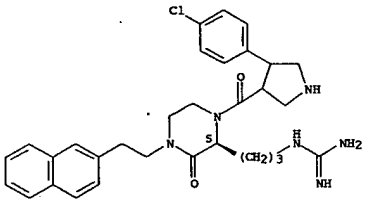
ACCESSION NUMBER: 2004:652533 HCAPLUS
DOCUMENT NUMBER: 141:191073
TITLE: Preparation of piperazines as melanocortin-specific agonists, antagonists, or mixed agonists and antagonists.
INVENTOR(S): Sharma, Shubh D.; Shi, Yi-qun; Wu, Zhijun; Rajpurohit, Ramesh
PATENT ASSIGNEE(S): Palatin Technologies, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 70 pp., Cont.-in-part of Appl. No. PCT/US02/25574.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 8
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004157264	A1	20040812	US 2004-762079	20040121
WO 2003013571	A1	20030220	WO 2002-US25574	20020812
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
WO 2005102340	A1	20051103	WO 2004-US1462	20040121
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2005130988	A1	20050616	US 2005-36282	20050114
US 2005124636	A1	20050609	US 2005-40838	20050121
US 2005176728	A1	20050811	US 2005-99814	20050405

PRIORITY APPLN. INFO.:

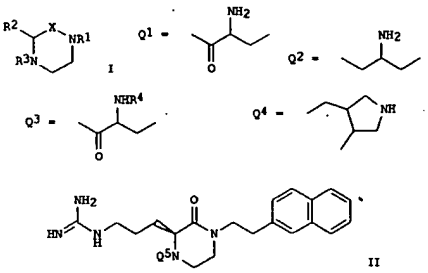
US 2001-311404P	P	20010810
WO 2002-US25574	A2	20020812
US 2003-474497P	P	20030530
US 2003-467442P	P	20030501
US 2004-536606P	P	20040114
US 2004-538100P	P	20040121
US 2004-761889	A2	20040121
US 2004-762079	A2	20040121
US 2004-546393P	P	20040219
US 2004-559741P	P	20040405
US 2004-563739P	P	20040419

L4 ANSWER 5 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



L4 ANSWER 5 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
US 2004-837519 A2 20040430

OTHER SOURCE(S): MARPAT 141:191073
GI



AB Title compds. [I; R1 = L1J, H; R2 = (CH2)yW, J, L1J; R3 = L2Q; L1 = (CH2)y, O(CH2)y, NH(CH2)y, CO(CH2)y, CO2(CH2)y, CH2CONH; J = (substituted) aryl, carbocyclyl, carbobicyclyl, heterobicyclyl; W = heteroatom unit with ≥1 cationic center, hydrogen bond donor, or hydrogen bond acceptor wherein ≥1 atom = N; L2 = Q1, Q2, Q3, Q4, etc.; Q = (substituted) Ph, naphthyl; R4 = H, R5, R5R6; R5 = amino acid residue, amine capping group; R6 = H, amine capping group; y = 1-6], were prepared Thus, title compound (II; Q5 = 2,4-dichloro-D-phenylalanyl) (general preparation given) at 1
μM gave 95% inhibition of melanocortin MC4-R.
IT 738600-02-7P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of piperazines as melanocortin-specific agonists, antagonists, or mixed agonists and antagonists)
RN 738600-02-7 HCAPLUS
CN Piperazinone, 3-[3-[(aminoiminomethyl)amino]propyl]-4-[[4-(4-chlorophenyl)-3-pyrrolidinyl]carbonyl]-1-[2-(2-naphthalenyl)ethyl]-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 6 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:221465 HCAPLUS
DOCUMENT NUMBER: 138:255249
TITLE: Preparation of piperazine and homopiperazine compounds useful in the treatment of thrombosis and to inhibit ADP-mediated platelet aggregation
INVENTOR(S): Levy, Daniel E.; Smyth, Mark S.; Scarborough, Robert M.
PATENT ASSIGNEE(S): Millennium Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 260 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003022214	A2	20030320	WO 2002-US28618	20020906
WO 2003022214	A3	20040325		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003153556	A1	20030814	US 2002-237153	20020906

PRIORITY APPLN. INFO.:

US 2001-317192P	P	20010906

OTHER SOURCE(S): MARPAT 138:255249
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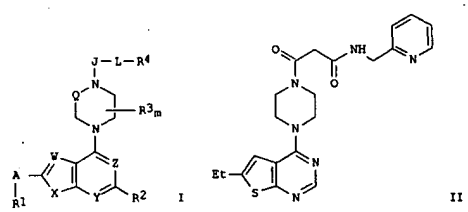


AB Piperazine and homopiperazine compds. I, wherein Q is (CH2)n; n is 1, 2; m is 0-4; W is N, CR5; X is S, O, NR6; Y is N, CR7; Z is N, CR8; J is CO, CS, CNR9, SO, SO2; A is O, S, NR10, CO, CH(OH); L is a direct link or a divalent linker; R1 is H, halo, CN, NO2, N3, alkyl, cycloalkyl, alkene, alkyne; R2 is H, halo, CN, NO2, N3, alkyl, cycloalkyl, alkene, alkyne,

L4 ANSWER 6 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
acyl; R3 is alkyl, cycloalkyl, acyl; R4 is H, F, CF3, CN, N3, NO2, alkyl, amino, alkylamino, cycloalkyl, heterocycloalkyl, heteroalkyl, fused bicycloalkyl, fused bicycloalkaryl, fused bicycloaryl; R5-R8 are independently H, alkyl, cycloalkyl; R9 is H, CN, NO2, alkyl; R10 is H, alkyl, acyl; are provided having a piperazine or homopiperazine ring which are useful in the treatment of thrombosis. Thus piperazine II was prepd. and tested in.vitro to inhibit ADP-mediated platelet aggregation (activity ranges are: > 20 μmol; 10-20 μmol; and < 10 μmol).

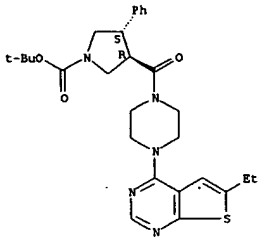
IT **502647-80-5P 502647-82-7P 502648-62-6P**
502648-64-8P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of piperazine and homopiperazine compds. useful in treatment of
thrombosis and to inhibit ADP-mediated platelet aggregation)

RN 502647-80-5 HCAPLUS
CN 1-Pyrrolidinecarboxylic acid, 3-[[4-(6-ethylthieno[2,3-d]pyrimidin-4-yl)-1-piperazinyl]carbonyl]-4-phenyl-, 1,1-dimethylethyl ester, (3R,4S)-rel-, trifluoroacetate (9CI) (CA INDEX NAME)

CM 1

CRN 502647-79-2
CMF C28 H35 N5 O3 S

Relative stereochemistry.



CM 2

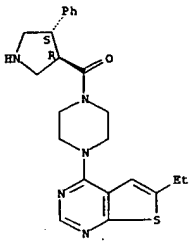
CRN 76-05-1
CMF C2 H F3 O2

RN 502647-82-7 HCAPLUS
CN Piperazine, 1-(6-ethylthieno[2,3-d]pyrimidin-4-yl)-4-[[(3R,4S)-4-phenyl-3-pyrrolidinyl]carbonyl]-, rel-, trifluoroacetate (9CI) (CA INDEX NAME)

CM 1

CRN 502647-81-6
CMF C23 H27 N5 O S

Relative stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

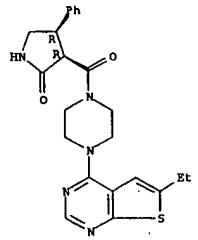
RN 502648-62-6 HCAPLUS
CN Piperazine, 1-(6-ethylthieno[2,3-d]pyrimidin-4-yl)-4-[[(3R,4R)-2-oxo-4-phenyl-3-pyrrolidinyl]carbonyl]-, rel-, trifluoroacetate (9CI) (CA INDEX

L4 ANSWER 6 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
NAME)

CM 1

CRN 502648-61-5
CMF C23 H25 N5 O2 S

Relative stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

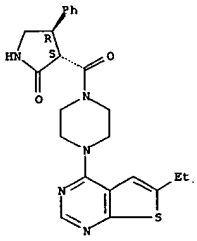
RN 502648-64-8 HCAPLUS
CN Piperazine, 1-(6-ethylthieno[2,3-d]pyrimidin-4-yl)-4-[[(3R,4S)-2-oxo-4-phenyl-3-pyrrolidinyl]carbonyl]-, rel-, trifluoroacetate (9CI) (CA INDEX NAME)

CM 1

CRN 502648-63-7
CMF C23 H25 N5 O2 S

Relative stereochemistry.

L4 ANSWER 6 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



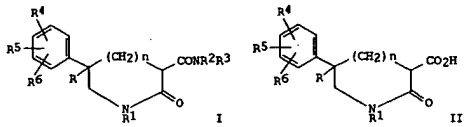
CM 2

CRN 76-05-1
CMF C2 H F3 O2

L4 ANSWER 7 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1978:152411 HCAPLUS
DOCUMENT NUMBER: 88:152411
TITLE: Heterocyclic amide derivatives
INVENTOR(S): Yuki, Hiroshi; Setoguchi, Nobuo
PATENT ASSIGNEE(S): Yoshitomi Pharmaceutical Industries, Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 6 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 52156859	A2	19771227	JP 1976-72457	19760618
PRIORITY APPLN. INFO.:			JP 1976-72457 A	19760618

GI

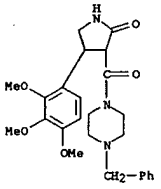


AB Thirty-five title derivs. I [R = H, Ph, pyridyl; R1 = H, alkyl, aralkyl; R2, R3 = H, alkyl, aralkyl, Ph, etc.; R2R3N may form a ring; R4, R5, R6 = H, alkyl, alkoxy, halo; R4 and R5 may be bound to form a methylenedioxy group; n = 0, 1] were prepared by reaction of II or their CO2H reactive derivs. with R2R3NH. I had antihypertensive, vasodilating, antithrombotic, analgesic, and anti-inflammatory activities (no data). Thus, a mixture of 9.2 g 3-(ethoxycarbonyl)-4-phenyl-2-pyrrolidone and 4.2 g piperidine in xylene was refluxed 46 h to give 8 g I (R = R1 = R4 = R5 = R6 = H, R2R3N = piperidino, n = 0).

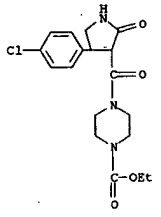
IT **62836-29-7P 62836-31-1P 62836-36-6P**
62836-40-2P 62836-44-6P 62836-45-7P
66157-97-9P 66158-01-8P 66158-02-9P
66158-09-6P 66178-96-9P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

RN 62836-29-7 HCAPLUS
CN Piperazine, 1-[(1-methyl-2-oxo-4,4-diphenyl-3-pyrrolidinyl)carbonyl]-4-(phenylmethyl)-, monohydrochloride (9CI) (CA INDEX NAME)

L4 ANSWER 7 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

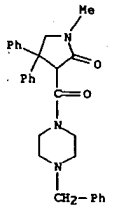


RN 62836-40-2 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-[[4-(4-chlorophenyl)-2-oxo-3-pyrrolidinyl]carbonyl]-, ethyl ester (9CI) (CA INDEX NAME)



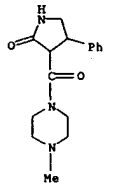
RN 62836-44-6 HCAPLUS
CN Piperazine, 1-[(1-methyl-2-oxo-4,4-diphenyl-3-pyrrolidinyl)carbonyl]-4-(2-methylphenyl)- (9CI) (CA INDEX NAME)

L4 ANSWER 7 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



● HCl

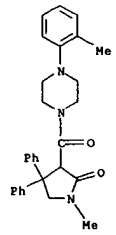
RN 62836-31-1 HCAPLUS
CN Piperazine, 1-methyl-4-[(2-oxo-4-phenyl-3-pyrrolidinyl)carbonyl]-, monohydrochloride (9CI) (CA INDEX NAME)



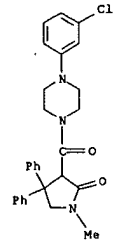
● HCl

RN 62836-36-6 HCAPLUS
CN Piperazine, 1-[[2-oxo-4-(2,3,4-trimethoxyphenyl)-3-pyrrolidinyl]carbonyl]-4-(phenylmethyl)- (9CI) (CA INDEX NAME)

L4 ANSWER 7 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

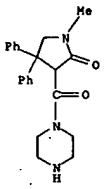


RN 62836-45-7 HCAPLUS
CN Piperazine, 1-(3-chlorophenyl)-4-[(1-methyl-2-oxo-4,4-diphenyl-3-pyrrolidinyl)carbonyl]- (9CI) (CA INDEX NAME)



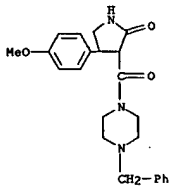
RN 66157-97-9 HCAPLUS
CN Piperazine, 1-[(1-methyl-2-oxo-4,4-diphenyl-3-pyrrolidinyl)carbonyl]-, monohydrochloride (9CI) (CA INDEX NAME)

L4 ANSWER 7 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



● HCl

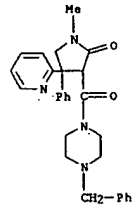
RN 66158-01-8 HCAPLUS
CN Piperazine, 1-[[4-(4-methoxyphenyl)-2-oxo-3-pyrrolidinyl]carbonyl]-4-(phenylmethyl)-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

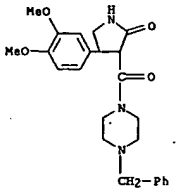
RN 66158-02-9 HCAPLUS
CN Piperazine, 1-[[4-(3,4-dimethoxyphenyl)-2-oxo-3-pyrrolidinyl]carbonyl]-4-(phenylmethyl)-, monohydrochloride (9CI) (CA INDEX NAME)

L4 ANSWER 7 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



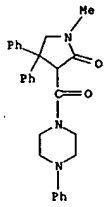
●2 HCl

L4 ANSWER 7 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



● HCl

RN 66158-09-6 HCAPLUS
CN Piperazine, 1-[(1-methyl-2-oxo-4,4-diphenyl-3-pyrrolidinyl)carbonyl]-4-phenyl- (9CI) (CA INDEX NAME)



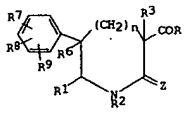
RN 66178-96-9 HCAPLUS
CN Piperazine, 1-[[1-methyl-2-oxo-4-phenyl-4-(2-pyridinyl)-3-pyrrolidinyl]carbonyl]-4-(phenylmethyl)-, dihydrochloride (9CI) (CA INDEX NAME)

L4 ANSWER 8 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1977:406018 HCAPLUS
DOCUMENT NUMBER: 87:6018
TITLE: Amides
INVENTOR(S): Yuki, Hiroshi; Setoguchi, Shinro
PATENT ASSIGNEE(S): Yoshitomi Pharmaceutical Industries, Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 9 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 51131870	A2	19761116	JP 1975-9020	19750120
PRIORITY APPLN. INFO.:			JP 1975-9020 A	19750120

GI



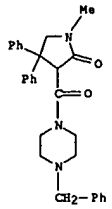
I, R=NR4R5
II, R=OH

AB Amides I (R1, R3 = H, alkyl; R2 = H, alkyl, aralkyl; R4, R5 = H, NH2, alkyl, dialkylamino, dialkylaminoalkyl, (substituted) Ph, aralkyl, PhNH, pyridyl, N-alkyl- or aralkyl 4-piperidyl; R4R5N may form a ring; R6 = H, (substituted) Ph; R7, R8, R9 = H, halo, alkyl, alkoxy; or R7R8 = OCH2O; Z = O, S; n = 0, 1) were prepared,by amidation of II or their CO2H reactive derivs. with HNR4R5. I are hypotensives, psychotropic agents, analgesics, or antiinflammatory agents (no data). Thus, reflux of a mixture of 9.2 g 3-ethoxycarbonyl-4-phenyl-2-pyrrolidone and 4.2 g piperidine in xylene 46 h gave 8 g 4-phenyl-3-piperidinocarbonyl-2-pyrrolidone. Among 19 addnl. I prepared were N-(2-dimethylaminoethyl)-1-methyl-2-oxo-4,4-diphenyl-3-pyrrolidinecarboxamide-HCl, 3-(4-benzylpiperazin-1-ylcarbonyl)-1-methyl-4,4-diphenyl-2-pyrrolidone-HCl, 3-(4-benzylpiperazin-1-ylcarbonyl)-1-methyl-5,5-diphenyl-2-piperidone, and 4-phenyl-3-(4-methylpiperazin-1-ylcarbonyl)-2-pyrrolidone-HCl.

IT **62836-29-7P 62836-31-1P 62836-36-6P**
62836-40-2P 62836-44-6P 62836-45-7P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

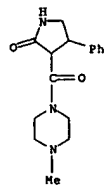
RN 62836-29-7 HCAPLUS
CN Piperazine, 1-[(1-methyl-2-oxo-4,4-diphenyl-3-pyrrolidinyl)carbonyl]-4-(phenylmethyl)-, monohydrochloride (9CI) (CA INDEX NAME)

L4 ANSWER 8 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



● HCl

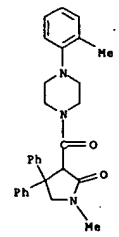
RN 62836-31-1 HCAPLUS
CN Piperazine, 1-methyl-4-[(2-oxo-4-phenyl-3-pyrrolidinyl)carbonyl]-, monohydrochloride (9CI) (CA INDEX NAME)



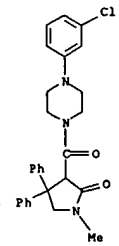
● HCl

RN 62836-36-6 HCAPLUS
CN Piperazine, 1-[[2-oxo-4-(2,3,4-trimethoxyphenyl)-3-pyrrolidinyl]carbonyl]-4-(phenylmethyl)- (9CI) (CA INDEX NAME)

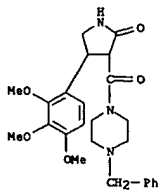
L4 ANSWER 8 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



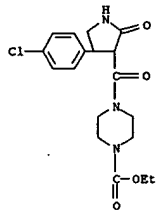
RN 62836-45-7 HCAPLUS
CN Piperazine, 1-(3-chlorophenyl)-4-[(1-methyl-2-oxo-4,4-diphenyl-3-pyrrolidinyl)carbonyl]- (9CI) (CA INDEX NAME)



L4 ANSWER 8 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



RN 62836-40-2 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-[[4-(4-chlorophenyl)-2-oxo-3-pyrrolidinyl]carbonyl]-, ethyl ester (9CI) (CA INDEX NAME)



RN 62836-44-6 HCAPLUS
CN Piperazine, 1-[(1-methyl-2-oxo-4,4-diphenyl-3-pyrrolidinyl)carbonyl]-4-(2-methylphenyl)- (9CI) (CA INDEX NAME)

L4 ANSWER 9 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1967:500020 HCAPLUS
DOCUMENT NUMBER: 67:100020
TITLE: Octahydro-3-oxoindolizinecarboxylates
INVENTOR(S): Mohrbacher, Richard J.
PATENT ASSIGNEE(S): McNeil Laboratories, Inc.
SOURCE: U.S., 6 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 3297704		19670110	US	19630802

GI For diagram(s), see printed CA Issue.

AB The title compds. I, where R1 was H or Ph and R2 was dialkylaminoalkyloxy, alkylpiperidyloxy, acylpiperazinyl, aralkylamino, pyridylalkylamino, hydroxyalkylamino, etc., were prepared by condensing the acid halide, mixed anhydride or alkyl ester of an octahydro-3-oxaindolizinecarboxylic acid with the appropriate tertiary amino alc. I possess hypotensive properties. The indolizinecarboxylic acids were prepared by the Knoevenagel condensation of 2-pyridinecarboxaldehyde with a dialkyl malonate in the presence of a basic condensing agent. The resulting dialkyl 2-pyridylmethylenemalonate was catalytically hydrogenated. The intermediate piperidinomethylmalonate cyclized to the octahydroindolizine ester which can be reacted with benzyl halide in the presence of NaH to give the corresponding 2-benzyl-2-indolizinecarboxylate. The latter may be saponified to the corresponding octahydro-3-oxo-indolizinecarboxylic acid.

The acid or acid chloride underwent cyclodehydration in the presence of inorg. acids to give hexahydrooxospiroindanindolizines. Complex metal hydride reduction of the latter gave hexahydro- or octahydro-hydroxyspiroindanindolizines which possessed anti-inflammatory properties. The use of a phenyl-substituted malonate prepared from dialkyl 2-pyridylmethylenemalonate and phenylmagnesium halide in the above reactions gave the 1-phenyl-substituted esters of octahydrooxoindolizine carboxylates or acids. The compds. had central nervous system depressant properties. Complex metal hydride reduction of I gave the corresponding alkyl amines. The presence of geometrical isomers caused the wide range of m.p. for some compds. A mixture of 2-pyridinecarboxaldehyde 107, dimethyl malonate 145, PhCO2H 6.6 g. and 8 ml. piperidine in C6H6 was heated for 2.5 hrs. with azeotropic removal of H2O. On cooling the mixture was concentrated in vacuo, diluted with Et2O, washed with aqueous NaHCO3, H2O and dried. Evaporation in vacuo and trituration of the residue with aqueous MeOH gave dimethyl 2-pyridylmethylenemalonate (II), m. 83.5-4.5° (aqueous MeOH). Diethyl 2-pyridylmethylenemalonate, b0.5 157°, and its sulfate, m. 100-1.5° (EtOH-Et2O) were also prepared To an Et2O solution of PhMgBr (prepared from PhBr 196 and Mg 30g.) at 0-5° was added dropwise a C6H6 solution of 125 g. II. After stirring 2 hrs. at 5° the mixture was poured into cold dilute HCl. The aqueous layer was removed and neutralized with K2CO3 to give dimethyl phenyl-2-pyridylmethylmalonate hydrochloride, m. 175-8° (decomposition) (EtOH-Et2O). The original filtrate from the HCl salt was made basic with K2CO3, extracted with Et2O and then with CH2Cl2. The

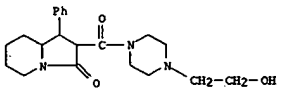
L4 ANSWER 9 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
exts. were concd. to give dimethyl phenyl-2-pyridylmethylmalonate (III), m. 97-8° (petroleum ether-EtOAc). Diethyl phenyl-2-pyridylmethylmalonate, m. 71.5-2°, was similarly prepd. II 22.1 g. was reduced over 1.25 g. PtO in a soln. 150 of ml. EtOH and 10 ml. HOAc at an initial H pressure of 60 psi. The catalyst was filtered off and the filtrate concd. and distd. to give methyl octahydro-3-oxo-2-indolizinecarboxylate (IV), bl 138-45° (a mixt. of isomers). The ethyl analog, b0.06 110-11°; and methyl octahydro-3-oxo-1-phenyl-2-indolizinecarboxylate (V), m. 84-9° (petroleum ether-EtOAc) were also prepd. A soln. of 29.6 g. IV in 50 ml. PhMe was added dropwise over 15 min. to a suspension of NaH (8.3 g. of 54.7% NaH in mineral oil washed well with PhMe) in 250 ml. PhMe. After refluxing 1 hr. a soln. of 25.3 g. PhCH2Cl in 50 ml. PhMe was added dropwise at 100°. The mixt. was refluxed 16 hrs., cooled and carefully treated with EtOH 5 and H2O 100 ml. The org. layer was washed with 10% NaOH, H2O and dil. HCl. The aq. acidic layer, concd. HCl and the combined aq. basic soln. were combined and adjusted to pH 3 to give octahydro-3-oxo-2-benzyl-2-indolizinecarboxylic acid (VI), m. 170° with gas evolution. The org. layer from the acid extn. was washed, and dried by azeotropic distn. and the resulting oil distd. to give methyl octahydro-3-oxo-2-benzyl-2-indolizinecarboxylate, b0.2 160°. To a soln. of 35 g. V in aq. MeOH was added 5 g. NaOH and the reaction refluxed 3 hrs. The soln. was concd., dild. with H2O and extd. with Et2O. The aq. layer was acidified with concd. HCl and extd. with CH2Cl2. Drying and evapn. in vacuo gave a mixt. of isomers of octahydro-3-oxo-1-phenyl-2-indolizinecarboxylic acid, m. 149-53° (EtOAc). Further recrystns. from EtOAc gave 1 isomer, m. 166-7°. Octahydro-3-oxo-2-indolizinecarboxylic acid (VII), m. 123-4.5° (Et2O-CH2Cl2) was prepd. To an Et2O suspension of 6.9 g. LiAlH4 was added an Et2O soln. of 10.6 g. V over 0.5 hr. The mixt. was refluxed 3.5 hrs. and cooled and 24.5 ml. H2O added. After filtration the filtrate was dried and concd. to a yellow oil. The oil was treated with fumaric acid in MeOH to give octahydro-1-phenyl-2-indolizinemethyl fumarate, m. 173-5° (decompn.) (iso-PrOH-Et2O). Also prepd. were octahydro-1-phenyl-2-indolizinemethanol methiodide (a mixt. of isomers), m. 218.5-19.5° (EtOH) and the single isomer, m. 184-6° (EtOH); and octahydro-2-benzyl-2-indolizinemethanol-HCl, m. 235-7° (iso-PrOH). A mixt. of dry NaOMe 0.2, octahydro-2-indolizinemethanol 6.8, and ethyl benzilate 10.6 g. in 700 ml. n-C7H16 was refluxed 1 hr. and distd. The residue was dissolved in 150 ml. Et2O and the soln. extd. with dil. HCl. The acidic aq. layer was made basic, and extd. with Et2O to give octahydro-2-indolizinemethyl benzilate, m. 104-6° (C7H16). Octahydro-1-phenyl-2-indolizinemethyl benzilate, m. 108-9° (C7H16) was similarly prepd. A mixt. of 7.2 g. VII and 1.6 g. NaOH in 50 ml. H2O-EtOH (3:2) was evapd. to a gum and dried at 60° in vacuo. A C6H6 soln. of β-(dimethylamino)ethyl chloride (prepd. by triturating 9.2 g. hydrochloride with NaOH) was added to a suspension of the dry Na carboxylate in 50 ml. C6H6. After refluxing 24 hrs. the mixt. was cooled, filtered and the filtrate evapd. to an oil. Distn. of the oil, b0.35 155°, and treatment with fumaric acid gave 2-(dimethylamino) ethyl octahydro-3-oxo-2-indolizinecarboxylate fumarate, m. 113-15° (95% EtOH-Et2O). Similarly prepd. was 2-(dimethylamino)ethyl octahydro-3-oxo-1-phenyl-2-indolizinecarboxylate fumarate, m. 161-3° (iso-PrOH-Et2O). To a soln. of NaOMe (prepd. from 0.57 g. Na in 50 ml. MeOH) was added a soln. of 19.7 g. IV in 50 ml. MeOH followed by a soln. of 15 g. d-amphetamine in 50 ml. MeOH and the mixt. refluxed 24

L4 ANSWER 9 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
hrs. and distd. to give octahydro-3-oxo-2-[N-(α-methylphenethyl)carbamoyl]indolizine, b0.075 185-92°. Also prepd. were octahydro-3-oxo-2-(4-phenyl-1-piperazinylcarbanyl)indolizine, m. 162-4° (EtOAc); and octahydro-3-oxo-2-[N-(2-dimethylaminoethyl)carbamoyl]indolizine, b0.35 174°, HCl, salt m. 174-6° [iso-PrOH-Et2O]. A C6H6 soln. of the acid chloride of VII prepd. from 8.1 g. VII via the anhyd. Na salt and 5.6 g. (COCl)2 by the procedure of Poas, et al. (CA 56: 14110g) was added dropwise over 25 min. to 5.2 g. 3-aminomethylpyridine. As a solid began to sep. 5 g. Et3N was added and the mixt. stirred overnight and filtered. The filtrate was washed, dried, and evapd. to give an oil. The aq. washing were combined, made pH 14 with 35% NaOH, and extd. with C6H6. The org. layer was dried and evapd. to give an oil. The combined oils were chromatographed on neutral Woelon Al2O3 and eluted with C6H6, Et2O, and Et2O-EtOH. The fraction eluted with Et2O-EtOH was evapd. and crystd. to give octahydro-3-oxo-2-[N-(3-pyridylmethyl)carbamoyl]indolizine, m. 115-16.5° (EtOAc-Et2O). Similarly prepd. were the following: (1-methyl-4-piperidyl)octahydro-3-oxo-1-phenyl-2-indolizinecarboxylate fumarate, m. 174-6° (EtOH-Et2O); octahydro-3-oxo-1-phenyl-2-(1-pyrolidinylcarbonyl)indolizine (VIII), m. 169-70° (EtOAc); octahydro-3-oxo-1-phenyl-2-(4-phenyl-1-piperazinylcarbonyl)indolizine, m. 164-5° (EtOAc); octahydro-3-oxo-1-phenyl-2-morpholinocarbonylindolizine, m. 128-9° (EtOAc); octahydro-3-oxo-1-phenyl - 2 - [4 - (2 - hydroxymethyl) - 1-piperazinylcarbonyl]indolizine, m. 179-80° (EtOAc); and (1-methyl - 4 - piperidyl)octahydro - 3 - oxo - 2 - indolizinecarboxylate fumarate. A C6H6 soln. of 6.6 g. VIII was added dropwise to a stirred Et2O suspension of 4.1 g. LiAlH4 and the mixt. refluxed 3 hrs. The complex was decompd. with 12 ml. H2O and filtered. The filtrate was dried, concd. and dissolved in Et2O. Satn. of the Et2O soln. with dry HCl gave octahydro-1-phenyl-2-(1-pyrrolidinylmethyl)indolizine-2HCl, m. 245.5-47° (EtOH-Et2O). Also prepd. were octahydro-1-phenyl-2-morpholinomethylindolizine-2HCl, m. 270-2° (decompn.); and octahydro-2-benzylindolizine, b0.15 97-100°, its hexamate, m. 108-20° (Me2CO-Et2O). VI was melted and heated until gas evaluation ceased. The oil was dissolved in Et2O-C6H6 and extd. with aq. NaHCO3. The org. layer gave octahydro-3-oxo-2-benzylindolizine, b0.175 138°. To 66 g. polyphosphoric acid at 100° was added 4.5 g. VI over 20 min. After 3 hrs. at 100°, the slurry was cooled and poured into crushed ice. The aq. soln. was extd. with Et2O-C6H6 and combined exts. gave 1',5',6',7',8',8a'-hexahydro-1-oxospiro(indan-2,2'-indolizin)-3'(2'H)-one (IX), m. 121-2° (C6H12). LiAlH4 redn. of IX gave octahydro-1-hydroxyspiro(indan-2,2'-indolizine), m. 110-22° (C6H6-C6H14). A soln. of 5.1 g. IX in 50 ml. iso-PrOH was added to a suspension of 0.76 g. NaBH4 in 125 ml. iso-PrOH at room temp. The mixt. was refluxed for 2 hrs., cooled in an ice bath and treated with 125 ml. 2.9M HCl. After removal of the iso-PrOH, the mixt. was extd. with Et2O-C6H6, to give an oil that partially cryst. on standing. The acidic aq. layer was made basic with 35% NaOH and extd. with CH2Cl2 to give an oil. The combined oils were crystd. from C6H6-n-C6H14 to give mixed cryst. form of 1',5',6',7',8',8a'-hexahydro - 1 - hydroxyspiro(indan - 2,2'- indolizine)-3'(2'H)-one (X), needles, m. 137-42° (cyclohexane); and prisms, m. 151-5° (cyclohexane). Concn. of the mother liquor from the recrystn. of the mixt. of stereisomers and recrystn. of the solid from cyclohexane gave a single isomer of X as

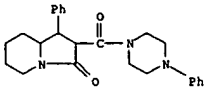
L4 ANSWER 9 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
irregular prisms, m. 154-6°. A mixed m.p. with the isomeric mixt. was depressed.

IT **3409-15-2P 6072-42-0P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

RN 3409-15-2 HCAPLUS
CN 1-Piperazineethanol, 4-[(octahydro-3-oxo-1-phenyl-2-indolizinyl)carbonyl]-(7CI, 8CI) (CA INDEX NAME)



RN 6072-42-0 HCAPLUS
CN Piperazine, 1-[(octahydro-3-oxo-1-phenyl-2-indolizinyl)carbonyl]-4-phenyl-(7CI, 8CI) (CA INDEX NAME)



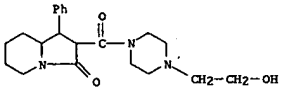
L4 ANSWER 10 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1967:37950 HCAPLUS
DOCUMENT NUMBER: 66:37950
TITLE: Indolizine derivatives
INVENTOR(S): Mohrbacher, Richard J.
PATENT ASSIGNEE(S): McNeil Laboratories, Inc.
SOURCE: U.S., 6 pp. Division of U.S. 3245990
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 3268535		19660823	US	19650614

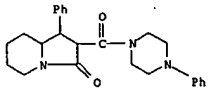
GI For diagram(s), see printed CA Issue.
AB Division of U.S. 3,245,990 (CA 64, 19563e). Title compds. where R is H or Ph and R1 is Ph or hydroxyalkyl were prepared by treating an indolizinecarboxylic acid ester or the acid chloride with substituted piperazines. Thus, a mixture of 5 parts Na octahydro-3-oxo-1-phenyl-2-indolizinecarboxylate, 2.6 parts oxallyl chloride, and 5 parts 1-phenylpiperazine was stirred at room temperature for 2 hrs., washed with dilute HCl, and dried to give ocrahydro-3-oxo-1-phenyl-2-(4-phenyl-1-piperazinylcarbonyl)indolizine, m. 164-5° (EtOAc). Other I prepared were (R, R1, and m.p. given): H, Ph, 162-4° (EtOAc); and Ph, HOCH2CH2, 179-80° (EtOAc). I are useful as anti-inflammatory and hypotensive agents.

IT **3409-15-2P 6072-42-0P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

RN 3409-15-2 HCAPLUS
CN 1-Piperazineethanol, 4-[(octahydro-3-oxo-1-phenyl-2-indolizinyl)carbonyl]-(7CI, 8CI) (CA INDEX NAME)



RN 6072-42-0 HCAPLUS
CN Piperazine, 1-[(octahydro-3-oxo-1-phenyl-2-indolizinyl)carbonyl]-4-phenyl-(7CI, 8CI) (CA INDEX NAME)

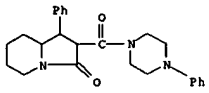


L4 ANSWER 11 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1967:2475 HCAPLUS
DOCUMENT NUMBER: 66:2475
TITLE: Octahydro-3-oxoindolizines
INVENTOR(S): Mohrbacher, Richard J.
PATENT ASSIGNEE(S): McNeil Laboratories, Inc.
SOURCE: U.S., 6 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

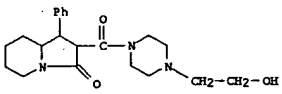
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 3274202		19660920	US	19630402

GI For diagram(s), see printed CA Issue.
AB Compds. of structure I were prepared Some of the products exhibited hypotensive and central nervous system depressant activity. A Knoevenagel condensation of 2-pyridinecarboxaldehyde 107 with CH2(CO2-Me)2 145 in the presence of piperidine and BzOH yields dimethyl 2-pyridylmethylenemalonate (II) 180 parts, m. 83.5-4.5° (aqueous MeOH). The diethyl analog (III) is similarly prepared (81%), b0.5 157°; sulfate m. 100-1.5° (EtOH-Et2O). Treatment of II 125 with PhMgBr in C6H6-Et2O at 0-5° afforded dimethyl phenyl-2-pyridylmethylmalonate (IV) 81 parts as HCl salt, m. 175-8° (decomposition) (EtOH-Et2O); free base m. 97-8° (petr. ether-EtOAc). Reduction of III 10.8 over PtO2 0.8 in absolute EtOH-AcOH at
60 psi. gave ethyl octahydro-3-oxo-2-indolizine-carboxylate (V) 8.9 parts, b0.06 110-11°. The dimethyl analog (VI) was analogously prepared, bl 138-45°. Similarly IV afforded methyl octahydro-3-oxo-1-phenyl-2-indolizinecarboxylate (VII) as an isomer mixture, m. 84-9° (petr. ether-EtOAc); treatment of octahydro-3-oxo-1-phenyl-2-indolizinecarboxylic acid (m. 166-7°) with CH2N2 afforded the methyl ester, m. 113.5-14.0° (petr. ether-EtOAc). The ir spectrum is very similar, but not identical to VII. Condensation of VII 29.6 and PhCH2Cl 25.3 with NaH in PhMe gave Me octahydro-3-oxo-2-benzyl-2-indolizinecarboxylate (VIII) 35.8 parts, b0.2 160°, and free acid 6.3 parts, m. 170° (decomposition). Saponification of VIII with NaOH in aqueous MeOH afforded the
free acid (as isomer mixture), m. 149-53° (EtOAc); repeated recrystn. yielded one isomer, m. 166-7°. Saponification of V gave 72% of the corresponding acid, m. 123-4.5° (Et2O-CH2Cl2). Hydrolysis of VIII 23 with 10% NaOH (aqueous EtOH) gave octahydro-3-oxo-2-benzyl-2-indolizinecarboxylic acid 16.9 parts, m. 177° (decomposition) (EtOAc). Reduction of VIII 10.6 with LiAlH4 yielded octahydro-1-phenyl-2-indolizinemethanol (IX) 8.5 parts; fumarate m. 173-5° (decomposition) (iso-PrOH-Et2O). Treatment of IX with MeI gave two methiodide fractions, one, an isomer mixture, m. 218.5-19.5° (EtOH); the other, a single isomer, m. 184-6°, with similar ir spectra. Octahydro-2-benzyl-2-indolizinemethanol-HCl (X), m. 235-7° (iso-PrOH), was similarly prepared from VIII. Octahydro-2-indolizinemethyl benzilate, m. 104-6° (n-heptane), was obtained from the corresponding amino alcohol and ethyl benzilate by transesterification; similarly IX yielded octahydro-1-phenyl-2-indolizinemethyl benzilate, m. 108-9° (hexane). Refluxing Na octahydro-3-oxo-2-indolizinecarboxylate 7.2 with

L4 ANSWER 11 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
CN Piperazine, 1-[(octahydro-3-oxo-1-phenyl-2-indolizinyl)carbonyl]-4-phenyl- (7CI, 8CI) (CA INDEX NAME)



L4 ANSWER 11 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
9.2 β-dimethylaminoethyl chloride in C6H6 24 hrs. yielded 2-dimethylaminoethyl octahydro-3-oxo-2-indolizinecarboxylate 7.3 parts, b0.35 155°; fumarate m. 130-115° (sic) (EtOH-Et2O). Similarly prepd. were: 2-dimethylaminoethyl octahydro-3-oxo-1-phenyl-2-indolizinecarboxylate fumarate, m. 161-3° (iso-PrOH-Et2O); (1-methyl-4-piperidyl) octahydro-3-oxo-1-phenyl-2-indolizinecarboxylate fumarate, m. 174-6° (EtOH-Et2O); octahydro-3-oxo-2-(4-phenyl-1-piperazinylcarbonyl)indolizine, m. 162-4° (EtOAc); octahydro-3-oxo-2-[N-(2-dimethylaminoethyl)carbamoyl]indolizine, b0.35 174° [HCl salt m. 174-6° (iso-PrOH-Et2O)]; octahydro-3-oxo-2-[N-(α-methylphenethyl)carbamoyl]indolizine, b0.075 185-92°. Prepg. the acid chlorides from the corresponding Na salts and (COCl)2 followed by reaction with the appropriate amine afforded: octahydro-3-oxo-2-[N-(3-pyridylmethyl)carbamoyl]indolizine, m. 115-16.5° (EtOAc-Et2O); octahydro-3-oxo-1-phenyl-2-(1-pyrrolidinylcarbonyl)indolizine, m. 169-70° (EtOAc); octahydro-3-oxo-1-phenyl-2-(4-phenyl-1-piperazinylcarbonyl)indolizine, m. 164-5° (EtOAc); octahydro-3-oxo-1-phenyl-2-morpholinocarbonylindolizine, m. 128-9° (EtOAc); octahydro-3-oxo-1-phenyl-2-[4-(2-hydroxymethyl)-1-piperazinylcarbonyl]indolizine, m. 178-80° (EtOAc). Octahydro-1-phenyl-2-(1-pyrrolidinylmethyl)indolizine dihydrochloride, m. 245.5-7.0° (EtOH-Et2O), was prepd. by LiAlH4 redn. of the corresponding oxo compd. Analogously prepd. were: octahydro-1-phenyl-1-morpholinomethylindolizine dihydrochloride, m. 270-2° (decompn.); octahydro-2-benzylindolizine, b0.15 97-100°; hexamate m. 108-120° (Me2CO-Et2O). Octahydro-3-oxo-2-benzyl-2-indolizinecarboxylic acid (XI) 70.6, yields on 10 min. heating as a melt 49.5 octahydro-3-oxo-2-benzylindolizine, b0.175 138°. Heating XI 4.5 with polyphosphoric acid 66 3 hrs. at 100° affords 1',5',6',7',8',8a'-hexahydro-1-oxospiro [indan-2,2'-indolizin]-3'(2'H)-one (XII) 4 parts, m. 121-2° (C6H12). Redn. of XII with LiAlH4 gave octahydro-1-hydroxyspiro [indan-2,2'-indolizine], m. 110-22° (C6H6-hexane). Redn. of XII 5.1 with NaBH4 in iso-PrOH yielded 1',5',6',7',8',8a'-hexahydro-1-hydroxyspiro[indan-2,2'-indolizine]-3'(2'H)-one 3.3 parts, m. 137-42°, and m. 151-5° (C6H12); the mother liquor yielded an addnl. 0.2 part second isomer; a mixed m.p. with the isomeric mixt. was depressed.
IT 3409-15-2P 6072-42-0P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 3409-15-2 HCAPLUS
CN 1-Piperazineethanol, 4-[(octahydro-3-oxo-1-phenyl-2-indolizinyl)carbonyl]- (7CI, 8CI) (CA INDEX NAME)



RN 6072-42-0 HCAPLUS

L4 ANSWER 12 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1966:482196 HCAPLUS
DOCUMENT NUMBER: 65:82196
ORIGINAL REFERENCE NO.: 65:15351d-h,15352a-c
TITLE: Octahydro-3-oxo-2-indolizinecarboxylic acids
INVENTOR(S): Mohrbacher, Richard J.
PATENT ASSIGNEE(S): McNeil Laboratories, Inc.
SOURCE: 6 pp.
DOCUMENT TYPE: Patent
LANGUAGE: Unavailable
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

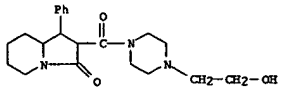
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 3268540		19660823	US	19650614

GI For diagram(s), see printed CA Issue.
AB Compds. of the general formula I, where R1 is H or PhCH2 and R2 is CO2H, CH2OH, or a carbamoyl or a carboalkoxy group, are prepared and can be used as hypotensive and antiinflammatory agents. Thus, a mixture of 107 parts 2-pyridinecarboxaldehyde, 145 parts CH2(CO2Me)2, 8 parts piperidine, 6.6 parts BzOH, and C6H6 is heated to give to give di-Me 2-pyridylmethylenemalonate (II), m. 83.5-4.5° (aqueous MeOH). Similarly prepared is di-Et 2-pyridylmethylenemalonate sulfate (III sulfate), m. 100-1.5° (EtOH-Et2O). A solution of PhMgBr (196 parts PhBr and 30 parts Mg) in Et2O is treated with a C6H6 solution of 125 parts II to give di-Me phenyl(2-pyridylmethyl)malonate, m. 97-8° (ligroine-EtOAc); HCl salt m. 175-8° (decomposition) (EtOH-Et2O). Similarly prepared is di-Et phenyl(2-pyridylmethyl)malonate, m. 71.5-2° (ligroine). III (10.8 parts) in a mixture of 100 parts EtOH and 4 parts HOAc is hydrogenated in the presence of 0.8 part Pt oxide to give 6.2 parts Et octahydro-3-oxo-2-indolinecarboxylate (IV), b0.06 110-11°. Similarly prepared are the following I (R1 = H; R, R2, and m.p. given): H, CO2Me, -- (b1 138-45°); Ph, CO2Me, 84-9° (ligroine-EtOAc). A solution of 29.6 parts I(R = R1 = H, R2 = CO2Me) in 50 parts PhMe is treated with 8.3 parts 54.7% NaH in mineral oil to give 15% I(R = H, R1 = PhCH2, R2 = CO2H), m. 170°, and I(R = H, R1 = PhCH2, R2 = CO2Me), b0.2 160°. A mixture of 35 parts I(R = Ph, R1 = H, R2 = CO2Me), 5 parts NaOH, and aqueous MeOH is refluxed to give I (R = Ph, R1 = H, R2 = CO2H) (V), m. 166-7° (EtOAc). I (R = Ph, R1 = H, R2 = CO2Me) (10.6 parts) is treated with 6.9 parts LiAlH4 to give I (R = Ph, R1 = H, R2 = CH2OH); fumarate m. 173-5° (decomposition) (iso-PrOH-Et2O); MeI salt, m. 218.5-19.5°. Similarly prepared is I (R = H, R1 = PhCH2, R2 = CH2OH) HCl salt, m. 235-7° (iso-PrOH). A mixture of 0.2 part NaOMe, 6.8 parts I (R = R1 = H, R2 = CH2OH), 700 parts n-heptane, and 10.6 parts Ph2C(OH)CO2Et is refluxed to give 6.8 parts I [R = R1 = H, R2 = CH2O2CC(OH)Ph2], m. 104-6° (heptane). Similarly prepared is I [R = Ph, R1 = H, R2 = CH2O2CC(OH)Ph2], m. 108-9° (hexane). V (6.8 parts) is treated with 1.05 parts NaOH to give I (R = Ph, R1 = H, R2 = CO2Na). Also prepared are the following I (R1 = H) (R, R2, and m.p. fumarate given): H, CO2CH2CH2NMe2, 113-15°; Ph, CO2CH2CH2NMe2, 161-3°; Ph, 1-methyl-4-piperidylcarbonyl, 174-6°; Ph, COCl, --. A mixture of 16.8 parts IV, a solution of 1.08 parts NaOMe in 165 parts MeOH, and 14.6 parts 4-phenylpiperazine is refluxed 28 hrs. to give 15.5 parts octahydro-3-oxo-2-(4-phenyl-1-piperazinylcarbonyl)indolizine, m. 162-4° (EtOAc). Also prepared are the following I (R1 = H) (R, R2, and m.p. given): H, CONHCH2CH2NMe2, -- (HCl salt m. 174-6°); H, CONHCHMeCH2Ph, -- (b0.075 185-92°); H, N-(3-pyridylmethyl)carbamoyl, 115-16.5°; Ph, 1-pyrrolidinylcarbonyl,

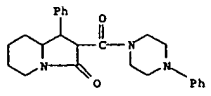
L4 ANSWER 12 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
169-70°; Ph, 4-phenylpiperazinocarbonyl, 164-5°; Ph, morpholinocarbonyl, 128-9° (EtOAc); Ph, 4-(2-hydroxyethyl)piperazinocarbonyl, 179-80° (EtOAc). I (R = Ph, R1 = H, R2 = pyrrolidinylcarbonyl) is treated with 4.1 parts LiAlH4 to give I (R = Ph, R1 = H, R2 = 1-pyrrolidinylmethyl)-2HCl m. 245.5-7° (EtOH ether). Similarly prepd. is I(R = Ph, R1 = H, R2 = morpholinomethyl)-2HCl, m. 270-2° (decompn.). I (R = H, R1 = PhCH2, R2 = CO2H) (VI) (70.6 parts) is heated to give 49.5 parts I(R = R2 = H, R1 = PhCH2) (VII), b0.275 138°. VII (15 parts) is treated with 7.4 parts LiAlH4 to give octahydro-2-benzylindolizine hexamate, m. 108-20° (Me2CO-Et2O). A mixt. of 4.5 parts VI and 66 parts polyphosphoric acid is heated 3 hrs. at 100° to give 2.8 parts 1',5',6',7',8',8a'-hexahydro-1-oxospiro(indan - 2,2'-indolizin)3'(2'H)-one (VIII), m. 121-2°. VIII (7.7 parts) is treated with 3.4 parts LiAlH4 to give 3 parts octahydro-1-hydroxyspiro(indan-2,2'-indolizine), m. 110-22° (C6H6-hexane). VIII (5.1 parts) in 50 parts iso-PrOH is added to 0.76 part NaBH4 in 125 parts iso-PrOH and the mixt. refluxed 2 hrs. to give 2.4 parts 1',5',6',7',8',8a'-hexahydro- 1-hydroxyspiro(indan-2,2'-indolizin)-3'(2'H)-one, m. 137-42° and 151-5°.

IT **3409-15-2**, 1-Piperazineethanol, 4-[(octahydro-3-oxo-1-phenyl-2-indolizinyl)carbonyl]- **6072-42-0**, Piperazine, 1-[(octahydro-3-oxo-1-phenyl-2-indolizinyl)carbonyl]-4-phenyl- (preparation of)

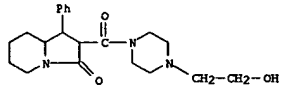
RN 3409-15-2 HCAPLUS
CN 1-Piperazineethanol, 4-[(octahydro-3-oxo-1-phenyl-2-indolizinyl)carbonyl]-(7CI, 8CI) (CA INDEX NAME)



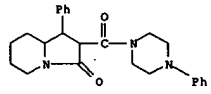
RN 6072-42-0 HCAPLUS
CN Piperazine, 1-[(octahydro-3-oxo-1-phenyl-2-indolizinyl)carbonyl]-4-phenyl-(7CI, 8CI) (CA INDEX NAME)



L4 ANSWER 13 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



RN 6072-42-0 HCAPLUS
CN Piperazine, 1-[(octahydro-3-oxo-1-phenyl-2-indolizinyl)carbonyl]-4-phenyl-(7CI, 8CI) (CA INDEX NAME)



L4 ANSWER 13 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1966:104086 HCAPLUS
DOCUMENT NUMBER: 64:104086
ORIGINAL REFERENCE NO.: 64:19563e-h
TITLE: 2-(Pyrrolidino and morpholino)carbonyl-3-oxooctahydroindolizines
INVENTOR(S): Mohrbacher, Richard J.
PATENT ASSIGNEE(S): McNeil Laboratories, Inc.
SOURCE: 6 pp.
DOCUMENT TYPE: Patent
LANGUAGE: Unavailable
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 3245990		19660412	US	19650614

GI For diagram(s), see printed CA Issue.

AB Dimethyl 2-pyridylmethylenemalonate (22.1 g.) in 150 ml. EtOH and 10 ml. AcOH in the presence of PtO2 was hydrogenated under 4 atmospheric H to give 14.3 g. methyl octahydro-3-oxo-2-indolizinecarboxylate (I, R = R1 = H, R2 = CO2Me), b1, 138-45°. A solution of 29.6 g. methyl octahydro-3-oxo-2-indolizinecarboxylate in 50 ml. PhMe was added during 15 min. to a suspension of 4.5 g. NaH in 250 ml. PhMe. Gas evolution stopped after refluxing 1 hr. A solution of 25.3 g. PhCH2Cl in 50 ml. PhMe was added to the stirred mixture at 100°. After 16 hrs. stirring at reflux the mixture gave 35.8 g. methyl octahydro-3-oxo-2-benzyl-2-indolizinecarboxylate (I, R = H, R1 = CO2Me, R2 = CH2Ph), b0.2 160°, and 6.3 g. octahydro-3-oxo-2-benzyl-2-indolizinecarboxylic acid (II), m. 170° (decomposition). During 20 min. 4.5 g. II was added to 66 g. polyphosphoric acid at 100°. After stirring 3 hrs. at 100° the mixture was worked up to give 4 g. III, m. 121-2° (cyclohexane). Also prepared were the following I (R, R1, R2, and m.p. or b.p.(mm.) given): H, CO2H, H, 123-4.5°; H, CO2H, CH2Ph, 177°; H, CO2Et, H, 110-11°(0.06); Ph, CO2H, H, 84-9°; H, CO2CH2CH2NMe2, H, 155°(0.35); Ph, 4-morpholinocarbonyl, H, 128-9°; Ph, 1-pyrrolidinylcarbonyl, H, 169-70°; H, CH2Ph, H, 138°(0.17). Also prepared was octahydro-2-benzyl-2-indolizinemethanol-HCl, m. 235-7°, and octahydro-1-phenyl-2-(1-pyrrolidinylmethyl)indolizine-2HCl, m. 245.5-47°. The indolizines of this patent have various pharmacol. activities, including hypotensive, antiinflammatory, and central nervous system depressant.

IT **3409-15-2**, 1-Piperazineethanol, 4-[(octahydro-3-oxo-1-phenyl-2-indolizinyl)carbonyl]- **6072-42-0**, Piperazine, 1-[(octahydro-3-oxo-1-phenyl-2-indolizinyl)carbonyl]-4-phenyl- (preparation of)

RN 3409-15-2 HCAPLUS
CN 1-Piperazineethanol, 4-[(octahydro-3-oxo-1-phenyl-2-indolizinyl)carbonyl]-(7CI, 8CI) (CA INDEX NAME)

L4 ANSWER 14 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1966:93375 HCAPLUS
DOCUMENT NUMBER: 64:93375
ORIGINAL REFERENCE NO.: 64:17557b-h,17558a-c
TITLE: Octahydroindolizines
INVENTOR(S): Mohrbacher, Richard J.
PATENT ASSIGNEE(S): McNeil Laboratories, Inc.
SOURCE: 6 pp.
DOCUMENT TYPE: Patent
LANGUAGE: Unavailable
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 3245991		19660412	US	19630402

GI For diagram(s), see printed CA Issue.

AB The title compds. (I), which possess hypotensive properties, antiinflammatory, and anticholinergic activity, were prepared, by the Knoevenagel condensation of 2-pyridinecarboxaldehyde (II) with a dialkyl malonate in the presence of a suitable condensing agent, and treating the resulting dialkyl 2-pyridylmethylenemalonate in a number of ways to produce the 1-Ph, and 2-PhCH2 substituted derivs. A mixture of 107 II, 145 CH2(CO2Me)2, 8 piperidine, and 6.6 parts BzOH was heated in C6H6 for 2.5 hrs. with azeotropic distillation of H2O to give 180 parts dimethyl 2-pyridylmethylenemalonate (III), m. 83.5-4.58° (aqueous MeOH). Similarly prepd. was diethyl 2-pyridinemethylenemalonate (IV), IV sulfate m. 100-1.5°. To an ethereal solution of PhMgBr (prepared from 196 PhBr and 30 parts Mg) was added dropwise during 1.5 hrs. at 0° to 5° a C6H6 solution of 125 parts III. The mixture was poured into cold dilute HCl and the aqueous layer worked up to give 81 parts dimethyl phenyl-2-pyridylmethylmalonate (V), m. 97-8°, V.HCl m. 175-8°. IV similarly gave the corresponding diethyl phenyl-2-pyridylmethylmalonate (VI), m. 71.5-2°. VI (10.8 parts) was reduced over 0.8 part Pt oxide in 100 parts EtOH and 4 parts AcOH at 60 psi. of H to give 6.2 parts Et octahydro-3-oxo-2-indolizinecarboxylate (VII), b0.06 110-11°. III was similarly reduced to Me octahydro-3-oxo-2-indolizinecarboxylate (VIII), b1 138-45°. An ethanolic solution of 10 parts V containing 10 parts AcOH was hydrogenated at room temperature in the presence of 1 part Pt oxide at 51 psi. of H to give Me octahydro-3-oxo-1-phenyl-2-indolizinecarboxylate (IX), m. 84-9° (IXa) and 113.5-14° (IXb). IXb was also obtained by treating octahydro-3-oxo-1-phenyl-2-indolizinecarboxylic acid (X), m. 166-7°, with CH2N2 in MeOH. A solution of 29.6 VIII in 50 PhMe was added dropwise during 15 min. to a suspension of NaH (8.3 parts 54.7% NaH in mineral oil) in 250 parts PhMe. The mixture was refluxed 1 hr. and treated dropwise with stirring at 100° with 25.3 PhCH2Cl in 50 parts PhMe. The mixture was stirred 16 hrs. at reflux, cooled, carefully treated with 5 parts absolute EtOH and 100 parts H2O. The organic layer was worked up to give 6.3 parts octahydro-3-oxo-2-benzyl-2-indolizinecarboxylic acid (XI), m. 170° (with gas evolution), and 35.8 parts of the Me ester (XII) of XI, b0.2 160°. An aqueous methanolic solution of 35 parts IX containing 5 parts NaOH was refluxed 3 hrs. to give a mixture of geometrical isomers of the free acid (X). Octahydro-3-oxo-2-indolizinecarboxylic acid (XIII), m. 123-4.5° was similarly obtained from its Et ester (VII). A mixture of 2.3 XII, 40 EtOH, and 50 parts 10% NaOH was refluxed 5 hrs. to give 16.9 parts XI. IX was

L4 ANSWER 14 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
reduced with 6.9 parts LiAlH4 and the recovered product treated with 1.2 parts fumaric acid in MeOH to give I fumarate (R = Ph, R' = H, n = 1, R2= OH), m. 173-5° (decompn.). An ethereal soln. of the above reduction product was treated with MeI for 50 hrs. to give the corresponding methiodide, m. 184-6° (one isomer), and m. 218.5-19.5° (mixt. of isomers). XII was similarly reduced to I.HCl (R = H, R1 = PhCH2, n =1, R2 = OH), m. 235-7°. A suspension of 0.2 NaOMe, 6.8 I (R = R1 = H, n = 1, R2 = OH) (Ia), and 10.6 Et benzilate in 700 parts n-heptane was refluxed 1 hr. to give 6.8 parts I [R = R1 = H, n = 1, R2 = OCOC(OH)Ph2], m. 104-6°. Similarly prepd. was I (R = Ph, R1 = H, n = 1, R2 = OCOC(OH)Ph2), m. 108-9°. A soln. of 7.2 XIII and 1.6 NaOH in 50 parts H2O-EtOH was evapd. and the dry residue, resuspended in 50 parts C6H6, was treated with a C6H6 soln. of Me2NCH2CH2Cl and refluxed 24 hrs. to give 2-dimethylaminoethyl octahydro-3-oxo-2-indolizinecarboxylate fumarate, m. 113-15°. Similarly prepd. was 2-dimethylaminoethyl octahydro-3-oxo-1-phenyl-2-indolizinecarboxylate fumarate, m. 161-3°. The acid chloride of X (prepd. from 6.5 parts of the Na salt and 2.9 parts oxalyl chloride) was added dropwise to a soln. of 3 parts 1-methyl-4-hydroxypiperidine in C6H6 and stirred 1 hr. at room temp. to give (1-methyl-4-piperidyl) octahydro-3-oxo-1-phenyl-2-indolizinecarboxylate fumarate, m. 174-6°. The following were similarly prepd. by the above procedures: octahydro-3-oxo-2-[4-phenyl-1-piperazinylcarbonyl) indolizine, m. 162-4°; octahydro-3-oxo-2-[N-(2-dimethylaminoethyl)carbamoyl]ind olizine, m. 174-6° (HCl salt); octahydro-3-oxo-2-[N-(α-methylphenethyl)carbamoyl]indolizine, b0.075 185-92°; octahydro-3-oxo-2-[N-(3-pyridylmethyl)carbamoyl]indolizine, m. 115-16.5°; octahydro-3-oxo-1-phenyl-2-(1-pyrrolidinylcarbonyl)indolizine, m. 169-70°; octahydro-3-oxo-2-(4-phenyl-1-piperazinyl-carbonyl)indolizine, m. 164-5°; octahydro-3-oxo-2-morpholino-carbonylindolizine, m. 128-9°; and octahydro-3-oxo-1-phenyl-2-[4-(2-hydroxymethyl)-1-piperazinylcarbonyl]indolizine, m. 179-80°. The following I derivs. were obtained by the procedures described above (R, R1, n, R2, and m.p. of the di-HCl salt given): Ph, H, 1, 1-pyrrolidinyl, 245.5-7°; and Ph, H, 1, morpholino, 270-2° (decompn.). XI (70.6 parts) was melted and heated 10 min. until no more gas evolved to give 49.5 parts octahydro-3-oxo-2-benzylindolizine (XIV), b0.175 138°. XIV (15 parts) was reduced in the usual manner with LiAlH4 and the recovered product converted to the hexamate salt of octahydro-2-benzylindolizine, m. 108-20°. XI (4.5 parts) was added portionwise during 20 min. to 66 parts polyphosphoric acid heated to 100°, and kept at 100° 3 hrs. with stirring to give 1',5',6',7',8',8'a-hexahydro-1-oxospiro(indan-2,2'-indolizin)-3'(2'H)-one (XV), m. 121-2°. XV was reduced with LiAlH4, as above to give octahydro-1-hydroxyspiro(indan-2,2'-indolizine), m. 110-22°. XV (5.1 parts) in 50 parts iso-PrOH was added rapidly to a suspension of 0.76 part NaBH4 in 125 parts 2-PrOH and the mixt. was refluxed 2 hrs. and worked up in the usual manner to give 2.4 parts 1',5',6',7',8',8'a-hexahydro-1-hydroxyspiro(indan-2,2'-indolizine)-3'(2'H)-one, m. 137-42° and m. 151-5°.

IT **5501-77-9**, 1-Piperazinemethanol, α-methyl-4-[(octahydro-3-oxo-1-phenyl-2-indolizinyl)carbonyl]- **6072-42-0**, Piperazine, 1-[(octahydro-3-oxo-1-phenyl-2-indolizinyl)carbonyl]-4-phenyl- (preparation of)

RN 5501-77-9 HCAPLUS

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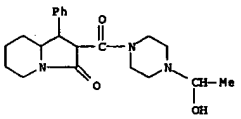
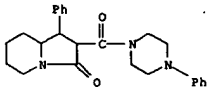
CN 1-Piperazinemethanol, α-methyl-4-[(octahydro-3-oxo-1-phenyl-2-indolizinyl)carbonyl]- (7CI, 8CI) (CA INDEX NAME)



RN 6072-42-0 HCAPLUS

CN Piperazine, 1-[(octahydro-3-oxo-1-phenyl-2-indolizinyl)carbonyl]-4-phenyl- (7CI, 8CI) (CA INDEX NAME)



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ACCESSION NUMBER: 1965:462961 HCAPLUS
DOCUMENT NUMBER: 63:62961
ORIGINAL REFERENCE NO.: 63:11513b-h,11514a-d
TITLE: Oxo- and hydroxyspiroindanindolizines
INVENTOR(S): Mohrbacher, Richard J.
PATENT ASSIGNEE(S): McNeil Laboratories, Inc.
SOURCE: 5 pp.
DOCUMENT TYPE: Patent
LANGUAGE: Unavailable
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 3189611		19650615	US	19630402

GI For diagram(s), see printed CA Issue.

AB Compds. of the general structure, in which R1 is H or oxo and R2 is H, oxo, OH, or OCOR, have hypotensive, antiedema, and antiinflammatory activity. A mixture of 107 g. 2-pyridinecarboxaldehyde (I), 147 g. CH2(CO2Me)2, 8 g. piperidine, and 6.6 g. BzOH in C6H6 heated 2.5 hrs. with azeotropic distillation of H2O, concentrated, diluted with Et2O, washed with NaHCO3 and H2O, dried, evaporated, and triturated with aqueous MeOH gave 180 g. 2-C5H4NCH: C(CO2Me)2 (II), m. 83.5-4.5° (aqueous MeOH). I and CH2(CO2Et)2 similarly gave 81% 2-C5H4NCH:C(CO2Et)2 (III), b0.5 157°; sulfate m. 100-1.5° (EtOH-Et2O). Addition of 125 g. II in C6H6 to PhMgBr (from 30 g. Mg and 196 g. PhBr) at 0-5° over 1.5 hrs., stirring 2 hrs. at 5°, pouring into dilute HCl, and partial neutralization of the aqueous layer with K2CO3 gave 81 g. 2-C5H4NCH2CPh(CO2Me)2.HCl,m. 175-8° (decomposition) (EtOH-Et2O); free base (IV) m. 97-8° (petroleum ether-EtOAc). III (51 g.) gave 35 g. 2-C5H4NCH2CPh(CO2Et)2 (V), m. 71.5-72° (petroleum ether). Hydrogenation of 22.1 g. II on 1.25 g. PtO2 in 150 ml. EtOH and 10 ml. HOAc gave 14.3 g. Me octahydro-3-oxo-2-indolizinecarboxylate (VI), b1 138-45°. Hydrogenation of 10.8 g. III gave 8.9 g. Et octahydro-3-oxo-2-indolizinecarboxylate (VII), b0.06 110-11°. Hydrogenation of 10 g. IV in EtOH and 10 ml. HOAc on 1 g. PtO2 gave a mixture of isomers of Me octahydro-3-oxo-1-phenyl-2-indolizinecarboxylate (VIII), m. 84-9° (petroleum ether-EtOAc). Action on 29.6 g. VI in 50 ml. PhMe by 4.5 g. NaH in 250 ml. PhMe, followed by 25.3 g. PhCH2Cl in 50 ml. PhMe 16 hrs. gave 6.3 g. octahydro-3-oxo-2-benzyl-2-indolizinecarboxylic acid (IX), m. 170° (gas evoln.) and 35.8 g. Me octahydro-3-oxo-2-benzyl-2-indolizinecarboxylate (X), b0.2 160°. Saponification of 35 g. VIII gave 29.3 g. mixed isomers of octahydro-3-oxo-1-phenyl-2-indolizinecarboxylic acid (XI) m. 149-53° (EtOAc). Several recrystns. of X from EtOAc gave a single geometrical isomer, white prisms, m. 166.7°. Saponification of VII gave a 72% yield of mixed isomers of octahydro-3-oxo-2-indolizinecarboxylic acid (XII), m. 110-21°, from which a pure isomer, m. 123-4.5° (Et2O-CH2Cl2) was obtained. Saponification of 23 g. X by 50 ml. 10% NaOH and 40 ml. 95% EtOH and the mixture refluxed 5 hrs. gave 16.9 g. IX, m. 177° (gas evoln.) (EtOAc). Et octahydro-3-oxo 1-phenyl-2-indolizinecarboxylate (13.2 g.) and 8.2 g. LiAlH4 in Et2O were refluxed 3.5 hrs., treated with 24.5 ml. H2O, filtered, dried (MgSO4), and concentrated to give 8.5 g. oil, octahydro-1-phenyl-2-indolizinemethanol (XIII).

Treatment of this oil with 5 g. MeI 50 hrs. gave 7.3 g. solid, fractional crystallization of which from EtOH gave two isomers of octahydro-1-phenyl-2-indolizinemethanol methiodide, 4.1 g., m. 218.5-19.5°, and 0.8 g., m. 184-6°. Similar redn. of 10.6 g. VIII with 6.9 g. LiAlH4, followed by treatment of the oil with fumaric acid in MeOH, gave octahydro-1-phenyl-2-indolizinemethanol fumarate, m. 173-5° (decompn.) (iso-PrOH-Et2O). Redn. of 14.4 g. X by 5.7 g. LiAlH4 and washing, drying, and concn. of the mixt., followed by HCl, gave octahydro-2-benzyl-2-indolizinemethanol hydrochloride, m. 235-7° (iso-PrOH). A mixt. of 6.8 g. octahydro-2-indolizinemethanol, 0.2 g. NaOMe, and 10.6 g. Et benzilate in 700 ml. C7H16 was refluxed 1 hr., concd., dild. with Et2O, and extd. with dil. HCl to give 6.8 g. octahydro-2-indolizinemethyl benzilate, m. 104-6°. Similar treatment of 9 g. XIII with 9.5 g. Et benzilate gave octahydro-1-phenyl-2-indolizinemethyl benzilate, m. 108-9°. The Na salt from 7.2 g. XII was refluxed 24 hrs. in C6H6 soln. of Me2NCH2CH2Cl to give 7.3 g. β-dimethylaminoethyl octahydro-3-oxo-2-indolizinecarboxylate, b0.35 155°; fumarate m. 113-15° (iso-PrOH-Et2O). Similarly obtained was β-dimethylaminoethyl octahydro-3-oxo-1-phenyl-1-indolizinecarboxylate, oil; fumarate m. 161-3° (iso-PrOH-Et2O). The acid chloride of XI (prepd. from 6.5 g. XI Na salt and 2.9 g. (COCl)2) and 3 g. 1-methyl-4-hydroxypiperidine in C6H6 gave 1-methyl-4-piperidyl octahydro-3-oxo-1-phenyl-2-indolizinecarboxylate, oil; fumarate m. 174-6° (EtOH-Et2O). 4-Phenylpiperazine (14.6 g.) added to 16.8 g. VII and 1.08 g. NaOMe in 165 ml. MeOH, and the mixt. refluxed 28 hrs. gave 15.5 g. octahydro-3-oxo-2-(4-phenyl-1-piperazinylcarbonyl)indolizine, m. 162-4° (EtOAc). Similarly, 16.8 g. VII and 14 g. Me2NCH2CH2NH2 gave 9.5 g. octahydro-3-oxo-2-[N-(2-dimethylaminoethyl)carbamoyl]indolizin e, b0.35 174°; hydrochloride m. 174-6° (iso-PrOH-Et2O); and 19.7 g. VI and 15 g. (+)-amphetamine gave octahydro-3-oxo-2-[N-(α-methylphenethyl)carbamoyl]indolizine, b0.075 185-92°. XI acid chloride (from 8.1 g. XI and 5.6 g. (COCl)2) and 5.2 g. 3-aminomethylpyridine gave 5.5 g. octahydro-3-oxo-2-[N-(3-pyridylmethyl)carbamoyl]indolizine, m. 115-16.5° (EtOAc-Et2O). Similarly prepd. were octahydro-3-oxo-1-phenyl-2-(1-pyrrolidinylcarbonyl)indolizine (XIV), m. 169-70° (EtOAc); octahydro-3-oxo-1-phenyl-2-(4-phenyl-1-piperazinylcarbonyl)indolizine, m. 164-5° (EtOAc); octahydro-3-oxo-1-phenyl-2-morpholinocarbonylindolizine (XV), m. 128-9° (EtOAc); and octahydro-3-oxo-1-phenyl2-[4-(2-hydroxymethyl)-1-piperazinylcarbonyl]indolizine, m. 179-80° (EtOAc). Action of 4.1 g. LiAlH4 on 6.6 g. XIV in Et2O 3 hrs., followed by 12 ml. H2O, filtration, concn., drying, and dry HCl treatment gave octahydro-1-phenyl-2-(1-pyrrolidinylmethyl)indolizine dihydrochloride, m. 245.5-47° (EtOH-Et2O). Redn. of XV by LiAlH4, followed by HCl, gave octahydro-1-phenyl-2-morpholinomethylindolizine dihydrochloride, m. 270-2° (decompn.). Thermal decarboxylation of 70.6 g. IX gave 49.5 g. octahydro-3-oxo-2-benzylindolizine, pale yellow-oil, b0.175 138°, redn. of which by LiAlH4 gave octahydro-2-benzylindolizine, b0.15 97-100°; hexamate m. 108-20° (Me2COEt2O). A mixt. of 4.5 g. IX and 66 g. polyphosphoric acid at 100° 3 hrs., poured onto crushed ice, and extd. with Et2OC6H6, gave 4 g. 1',5',6',7',8',8' α-hexahydro-1-oxospiro(indan-2,2'-indolizine)-3'(2'H)-one (XVI), m. 121-2° (cyclohexane). LiAlH4 (3.4 g.) and 7.7 g. XVI in 900 ml. Et2O, refluxed 20 hrs., cooled, mixed with 10.4 ml. H2O, filtered, extd. with 10% NaOH, washed, dried, and concd, gave 5.6 g. octahydro-1-hydroxyspiro(indan-2,1'-indolizine), m. 110-22° (C6H6-C6H14). Redn. of 5.1 g. XVI in 50 ml. iso-PrOH by 0.76 g. NaBH4 in 125 ml. isoPrOH in 2 hrs. refluxing, followed by 125 ml. 2.9M HCl, concn., extn. with Et2O-C6H6, gave 3.8 g. oil; and an addnl. 0.6 g. oil was obtained by adding 35% NaOH to the aq. layer, extg. with CH2Cl2, and concg. Recrystn. of the oil, first from C6H6-C6H14, then from cyclohexane-C6H14 then from

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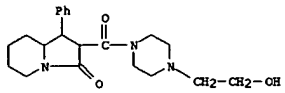
L4 ANSWER 15 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
cyclohexane ultimately gave 0.2 g. of a single isomer of 1',5',6',7',8',8'
a-hexahydro-1-hydroxyspiro(indan-2,2'-indolizine-)3'(2'H)-one, m.
154-6°.

IT 3409-15-2, 1-Piperazineethanol, 4-[(octahydro-3-oxo-1-phenyl-2-indolizinyl)carbonyl]-
(preparation of)

RN 3409-15-2 HCAPLUS

CN 1-Piperazineethanol, 4-[(octahydro-3-oxo-1-phenyl-2-indolizinyl)carbonyl]-
(7CI, 8CI) (CA INDEX NAME)



Andrew Freistein 10/788,859

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---Logging off of STN---

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Executing the logoff script...

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	81.97	243.51

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-9.49	-9.49

STN INTERNATIONAL LOGOFF AT 09:01:23 ON 14 NOV 2005